Improvement of Blood Pressure With Inhibition of the Epithelial Sodium Channel in Blacks With Hypertension

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The epithelial sodium channel (ENaC) is a critically important final regulator of the balance between intake and excretion of dietary sodium, and along with the thiazide-sensitive NaCl cotransporter, constitutes the predominant sodium transport systems in the aldosterone-sensitive distal nephron. As proposed by Guyton, and confirmed by the unraveling of the activating ENaC mutations in Liddle’s syndrome, dysregulation of the final balance of sodium intake and excretion can result in chronic volume expansion, plasma renin suppression, and arterial hypertension. Blacks often have low-renin, salt-sensitive hypertension, which could be explained by some sort of persisting activation of ENaC, even in the face of relative excess dietary salt intake. The possibility that polymorphisms in the 3 ENaC subunits could contribute to this apparent activation of ENaC and the utility of amiloride as an ENaC blocker in black hypertension have been considered previously.

In this issue of journal, Saha et al describe a systematic investigation of the effects of amiloride, spironolactone, and their use in combination in a short-term, randomized, placebo-controlled crossover study in blacks with established low-renin hypertension. As such, these studies represent an important extension of the previous work of this group published in Hypertension. Both agents block the effects of aldosterone on the aldosterone-sensitive distal nephron, with amiloride directly interacting with ENaC and spironolactone affecting all aldosterone-sensitive systems, including ENaC and the thiazide-sensitive NaCl cotransporter. Of note, the 98 black subjects in this report were hypertensive despite treatment that included thiazides and calcium channel blockers. Amiloride and spironolactone significantly reduced systolic blood pressure, but only amiloride significantly reduced diastolic blood pressure with the modest doses used in this study (10 mg amiloride and 25 mg spironolactone). There was a significant additive effect of the combination of amiloride and aldosterone antagonist on diastolic and systolic blood pressures.

That the effects of spironolactone were broader than inhibition of ENaC was demonstrated by a significant reduction in endothelin-1 levels. This may well be an important finding because there is greater endothelin-1–dependent vasoconstriction in black compared with white hypertensive subjects, as well as other vasodilatory responses to aldosterone antagonists in obesity, heart failure, and primary aldosteronism. Whether these effects of aldosterone antagonists are related to effects of aldosterone on the cardiovascular system is a question for further research.

The effects of amiloride and spironolactone on plasma aldosterone, plasma renin activity, and serum potassium levels should be emphasized. Amiloride, alone or in combination with spironolactone, caused a marked increase in the plasma aldosterone concentration, whereas there was only a mild increase in plasma aldosterone seen with spironolactone, and that likely was attributable to increases in serum potassium levels. The observation that amiloride and triamterene increase plasma aldosterone levels was noticed nearly 40 years ago. The more striking increase in plasma aldosterone with amiloride compared with spironolactone appears to be related to the increased plasma renin activity caused by amiloride that then promoted more aldosterone secretion. This effect of amiloride on plasma renin activity appears to be a short-term effect that is independent of any changes in extracellular volume, but the mechanism whereby amiloride stimulates plasma renin activity has not been defined. A direct effect of amiloride on the macula densa or the renin-containing granules of the afferent arteriole would be of interest but has not been explored.

As pointed out by Saha et al, the synergistic effects of amiloride and spironolactone may permit lower doses of each agent to be used in combination and therefore decrease the side effect profile of larger doses of either agent. Hyperkalemia is an important limiting side effect, especially if multiple inhibitors of the renin-angiotensin-aldosterone system are used. The possibility that amiloride may directly stimulate renin activation or release could open up new therapeutic possibilities because stimulation of renin activity increases aldosterone secretion, which enhances potassium secretion, whereas the direct effect of amiloride to block ENaC limits potassium secretion. It could useful to tease apart the effects of the amiloride analogues on renin activation to see if they could be distinguished from their direct effects on ENaC.

Despite the current enthusiasm for pharmacogenomic approaches and rigorous mathematical descriptions of polygenetic traits such as hypertension, the need for empiric approaches to complex biologic systems remains, and the carefully performed studies by Saha et al provide important insights into the possible role of dysregulation of ENaC in the pathogenesis of low renin hypertension in blacks.
References


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Hypertension. 2005;46:469-470; originally published online August 22, 2005;
doi: 10.1161/01.HYP.0000179583.64413.c1
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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